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Modeling and Control of the Cobelli Model as a Personalized Prescriptive Tool for Diabetes Treatment

by

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MODELING AND CONTROL OF THE COBELLI MODEL AS A PERSONALIZED PRESCRIPTIVE TOOL FOR DIABETES TREATMENT

by

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14. ABSTRACT

Mathematical models of glucose and insulin dynamics within the body allow for a more quantified approach in medicine prescription as well as a deeper understanding of the discrete operations of diabetes. Cobelli et. al. developed a mathematical model of glucose and insulin interactions that illustrate the dynamics from ingestion to absorption within the body. The FDA has approved this model to be a substitute for animal trials in preclinical testing due to its physiological accuracy. A physiological accurate model allows for the use of control theory to investigate applications as a personalized prescription tool.

This research developed a clinically-relevant, personalized algorithm for a diabetic patient that prescribes doses of oral medications, secretagogues and/or sensitizing agents, and inject insulin, slow or fast acting, based on their measured blood glucose levels. The research expanded upon Cobelli's mathematical model to include the four different medications and their effects on the body at a physiological level. A cost function was also developed to be utilized with Model Predictive Control (MPC) to adequately choose medications for future dosing based on physiological accuracy and convenience. A proof of concept demonstrated the possibility of the use of MPC for three medication inputs to control glucose levels. This work provided a framework for data verification once clinical data is obtained.

15. SUBJECT TERMS

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Abstract:

The human body maintains homeostasis with the assistance of hormones secreted by the endocrine system in order to sustain normal bodily functions. Glucose provides energy for these functions; however unhealthy levels lead to various health complications. In patients with diabetes, the body ineffectively utilizes insulin to assist the uptake and transport of glucose from the blood into the cells. In type I diabetes, the pancreas does not secrete enough insulin to assist the uptake of glucose. Type II diabetes occurs when cells in the body become desensitized to insulin. In both cases, glucose is transferred from the blood to the cells at a lower rate which increases the overall amount of glucose.

Mathematical models of glucose and insulin dynamics within the body allow for a more quantified approach in medicine prescription as well as a deeper understanding of the discrete operations of diabetes. Cobelli et. al. developed a mathematical model of glucose and insulin interactions that illustrate the dynamics from ingestion to absorption within the body. The FDA has approved this model to be a substitute for animal trials in preclinical testing due to its physiological accuracy. A physiological accurate model allows for the use of control theory to investigate applications as a personalized prescription tool.

This research developed a clinically-relevant, personalized algorithm for a diabetic patient that prescribes doses of oral medications, secretagogues and/or sensitizing agents, and inject insulin, slow or fast acting, based on their measured blood glucose levels. The research expanded upon Cobelli's mathematical model to include the four different medications and their effects on the body at a physiological level. A cost function was also developed to be utilized with MPC to adequately choose medications for future dosing based on physiological accuracy and convenience. A proof of concept demonstrated the possibility of the use of Model Predictive Control for three medication inputs to control glucose levels. This work provided a framework for data verification once clinical data is obtained.

Keywords: secretagogues, metformin, sensitizing agent, glucose, diabetes, model, predictive

Enclosures: (1) Cobelli Block Diagram
(2) Cobelli Equations
(3) Cobelli Parameters
(4) Metformin Ordinary Differential Equations
(5) Model Predictive Metformin Trail
(6) Random Patient Parameter Simulation Verification Test
(7) Metformin and Slow-acting Insulin Timing Tests

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This research endeavor integrates the combined efforts of advisors and a previous graduates. I would like to thank Professor Richard O'Brien in providing support and guidance throughout this year. He provided the mentorship during the moments when researching was at its most tenuous. I would also like to thank Captain Owen Thorp for introducing me to this research. Additionally, I would like to thank all those who supported me for the past year and a half.

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Glucose, Insulin, and Diabetes

Glucose is fundamental for cell growth and important physiological functions. It is the catalyst that begins glucose catabolism[1] which is where cells obtain most of their energy. Glucose is ingested into the body through various consumed foods, since glucose is a part of almost every food group and type. Once glucose is ingested it is then absorbed into the plasma from the gastro-intestinal system through the use of villi. The increase in blood glucose concentration within the body signals beta cells within the pancreas to begin secreting insulin. Insulin is then delivered from the pancreas into the liver which is then secreted into the blood. Insulin promotes glucose uptake by acting as the key to unlock the cell and allow glucose to enter within the cell. However, glucose-insulin interactions are not usually complication-free and can lead to a variety of symptoms.

Diabetes is a growing problem in America and the number of Americans affected by the ailment is slowly increasing. For people with Diabetes, the transfer of glucose from the bloodstream into cells is decreased which makes it no longer as efficient as it should be for human energy consumption. Type I Diabetes results in the pancreas producing insufficient insulin to transfer the necessary glucose from the blood to the cells. Type II Diabetes is a condition where cells are less sensitive to insulin and thus the transfer of glucose is less effective. As of the 2014 National Diabetes Statistics Report 29.1 million people have diabetes (9.3% of the population), and the number is only increasing [1]. Regardless of the type of diabetes, either conditions can lead to health complications such as heart disease, stroke, high blood pressure, blindness, kidney failure, and nervous system damage. Metformin is one of the medications that reduce the effects of diabetes by sensitizing muscles to insulin and reducing the amount of glucose that is absorbed by the body through meals [2].

Current Treatment and Research Contribution

Medication	**Sensitizing agents** [2]	**Secretagogues**	**Insulin (Fast-or slow-acting)**
Utilization	Type II	Type II	Type I/II
Body Interaction	Increases cell sensitivity to insulin	Forces pancreas to release more insulin	Increases insulin concentration in the blood

Table 1: Diabetics Medications

Diabetic patients take oral and/or injected medications in various assortments rather than just a single medication. Table 1 summarizes the medications commonly prescribed for diabetics and their effect on the body. Most diabetic patients treat their diabetes by monitoring their blood glucose and administering oral medications and/or injected insulin based on physician instructions. An active area of research for the treatment of diabetes is the development of an artificial pancreas [3,4,5]. Such a device would monitor blood glucose levels and administer insulin and possibly other medications autonomously. As an intermediate step in the diabetes treatment spectrum, the proposed project offers the patient assistance in determining when and

[1] Catabolism - the breakdown of complex molecules in living organisms to form simpler ones, releasing energy

how much to take of each medication while leaving the blood glucose monitoring and application of the prescribed medications to the patient.

The overarching goal of this research was to develop a clinically-relevant, personalized algorithm for a diabetic patient that prescribes doses of oral medications (secretagogues and/or sensitizing agents) and inject insulin (slow or fast acting) based on their measured blood glucose levels. This project builds upon previous projects in the Systems Engineering Department. The main contribution of the proposed project is the prescription algorithm, to provide a proof of concept in personalized prescription algorithm design. The most demanding challenge in the algorithm design is that four common treatments for diabetes in Table 1 have a similar effect to lower the blood glucose concentration. The redundancy of effort leads to a number of seemingly equivalent sequences of medication dosages. The algorithm will take into account the effect of each medication and commonly accepted limits on the amounts of medication that can be administered at any one time or over a longer period such as a day. The Model Predictive Control techniques to be discussed below will allow for a wide range of medication combinations that include, but are not limited to, the standard of physician prescription protocols. The goal is to consider the widest range of possibilities to find the best solution given the requirement of maintaining healthy blood glucose levels and the natural physiological constraints. Figure 1 shows a schematic (known as a block diagram) of the proposed algorithm. The proposed and current project utilizes the so-called Cobelli Model as a virtual patient.

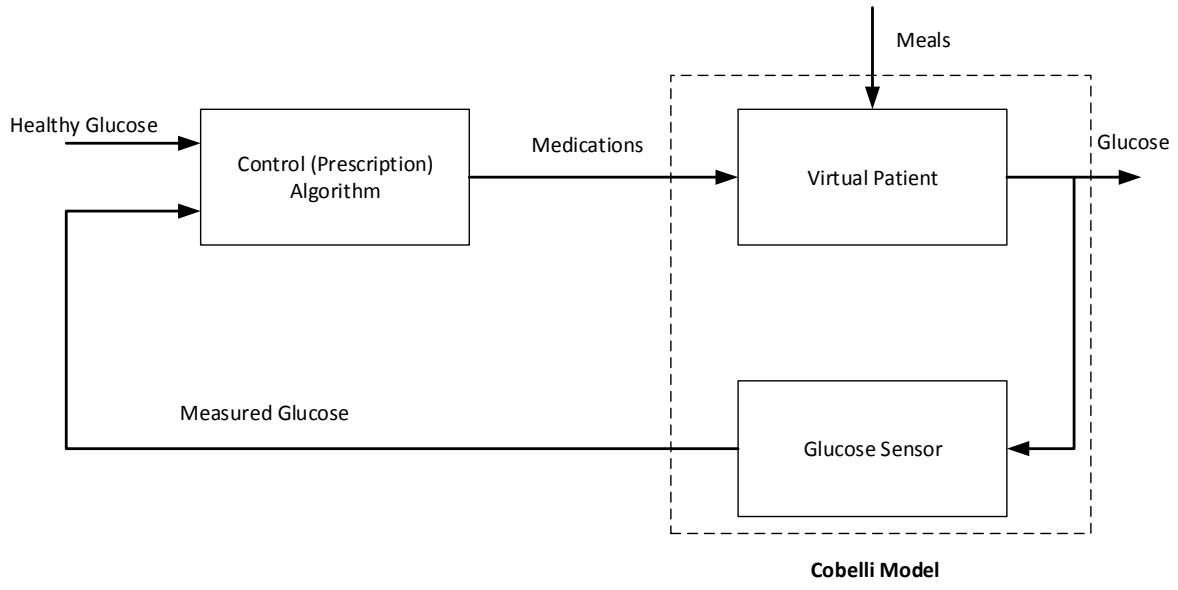

Figure 1: Schematic of diabetes treatment process

Cobelli Model

Claudio Cobelli and his team developed a simulation model of glucose and insulin interactions that illustrate the physiological events from ingestion of glucose to its absorption within the body [3]. The FDA has approved this model to substitute for animal trials in preclinical testing due to its physiological accuracy [3]. Cobelli utilized a "triple tracer meal protocol" to obtain model-independent measurements of glucose and insulin plasma concentration, glucose rate of appearance, and glucose utilization before a meal, during a meal, and after a meal [3]. Based on their results, Cobelli and his team were able to derive a set of differential equations and their relation to the various subsystems that utilized glucose and/or insulin. This model will serve as the virtual patient and controller model for the project. Figure 2 below represents the mathematical model of glucose and insulin as subsystems to represent the interaction between the different compartments within the human body. Enclosures (1) and (2) represent a larger visual of the interactions and equations of the Cobelli Model.

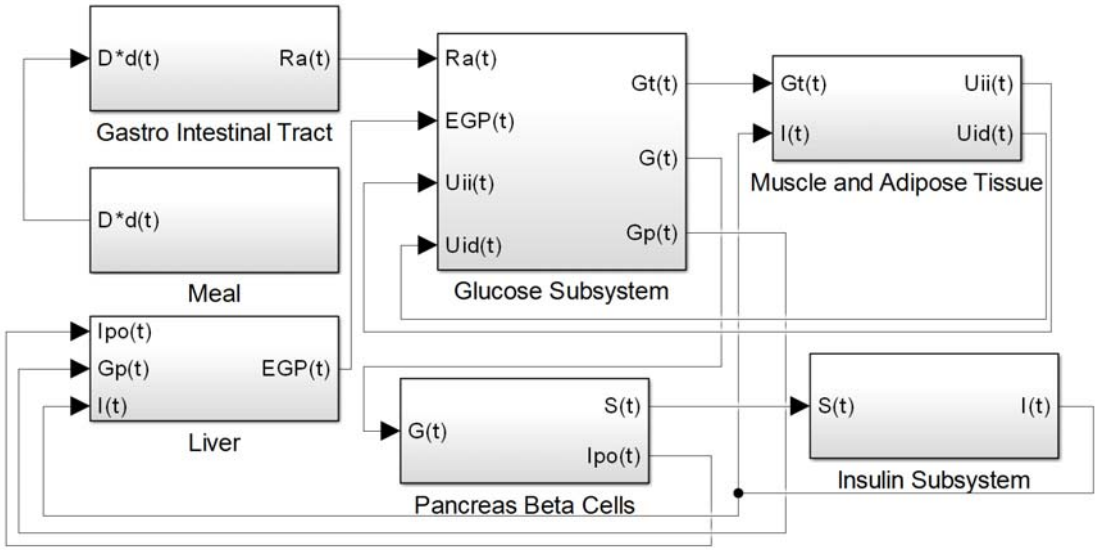

Figure 2: Simulink diagram of the mathematical model of glucose/insulin dynamics *[3]*

The diagram below, Figure 3, represents glucose interactions between blood plasma and tissue and the glucose kinetics in the body as it either absorbs glucose from meals, plasma, or from the external release from the liver. Renal extraction includes the amount of glucose lost through urine, while the variables k_1 and k_2 are both rate constants derived from data fitting. The glucose two-compartment subsystem is identified since it demonstrates a significant mediation target area. Overall the system involves glucose that rapidly equilibrates or slowly equilibrates with regard to the outgoing glucose for bodily function utilization or from liver glucose release.

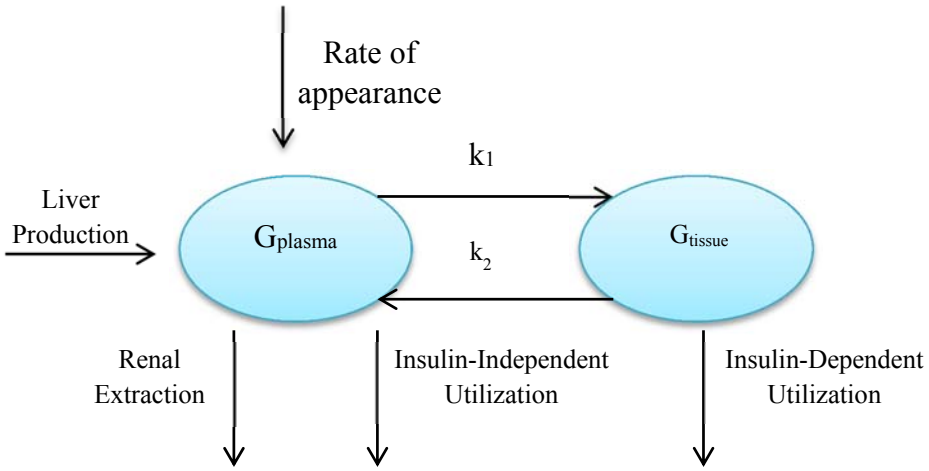

Figure 3: Glucose Two-Compartment Subsystem *[3]*

Control Methods

I. Model Predictive Control

Cobelli's model is an effective mathematical tool when used for diabetic tests that do not require immediate feedback or necessary control conditions. However, if the Cobelli model is to become a personalized prescriptive tool a control method is necessary to ensure accurate and safe medication dosages. Model predictive control, visualized in Figure 4, below, demonstrates the approach to its measurements and behavior modification. In succinct terms, model predictive control conditions inputs based on a "prediction" of what future outputs would be, utilizing the Cobelli model. The predicted input that provides the least amount of error from the desired result, based on iterations through an optimizing function that tries a variety of inputs, is then selected as the chosen input. The prediction algorithm does not just look ahead one step; rather it has a prediction horizon of several steps into the future, but only applies the next immediate step into the model. The prediction horizon is adjusted till the iteration of the model is complete or the simulation is ended.

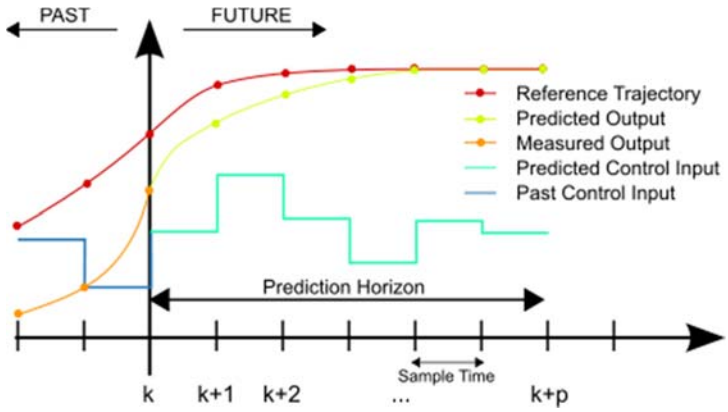

Figure 4: Model Predictive Control Algorithm with Time Sample Visual *[4]*

Dr. Magni demonstrated success with the application of model predictive control (MPC) to Cobelli's model to glucose dynamics with a linear model predictive controller and average population parameters [5]. The problem is that the differential equations of the Cobelli model are not linear and hence cannot be optimally controlled by linear MPC. A nonlinear MPC would have improved management on the dynamics and constraints given by glucose regulation within the body, opening opportunities for drug prescription when used in conjunction with an accurate model.

II. Adaptive Model Predictive Control

Adaptive model predictive control (AMPC) is an extension of MPC in that it updates the parameters of a simulation model with closed-loop feedback. The block schematic in Figure 5 below displays the closed-loop feedback process of AMPC when applied to the current revised Cobelli model. Previous Trident and Honors Systems Engineering research included a similar feedback loop, yet this proposal hopes to include a refined cost function algorithm, which will be discussed within the next section. Also, an in depth explanation will be given with regard to the other functional blocks. The block schematic works by measuring glucose levels from a patient as s/he ingests their original medication. Measurements taken from the patient are added to the patient's data sheet. The parameter adaptation algorithm uses the glucose and applied medication data in the past and simulates the model for different sets of parameters until it finds the set that best matches the previous output data. The parameter estimates are updated as each new glucose measurement is taken. Using the most recent parameter updates, the glucose control predicts the future using the Cobelli model. The input sequence is determined using the process in the figure below. Comparing Figure 1 to Figure 5, the Cobelli model acts as the Patient and generates the Patient Data. De-identified patient data may be available through Anne Arundel Medical Center (AAMC) and this data would be used instead of the Cobelli model output to compare the AMPC prescriptions to the AAMC physician prescriptions. The Control (Prescription) Algorithm block in Figure 1 incorporates the Parameter Adaption Algorithm and Model Predictive Controller blocks from Figure 5.

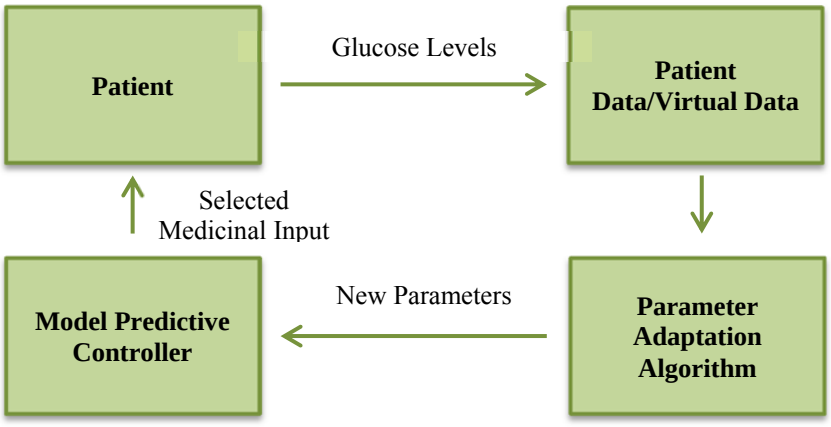

Figure 5: Flow diagram of a model predictive control within the Cobelli model.

Previous Sensitizing Agent Research

The most common sensitizing agent used by physicians is metformin and it will be the only sensitizing agent considered in this project. Metformin reduces the effects of Type II Diabetes by increasing cell sensitivity to insulin which in turn lowers blood glucose levels [6,7]. There are two pathways that metformin goes through to induce increased insulin sensitivities. The first pathway is by increasing the amount of insulin dependent glucose utilization in the body [6,7]. Through this pathway, glucose utilization increases toward healthy levels. The second pathway is by decreasing the endogenous glucose production of the liver to the bloodstream [6,7]. Reducing the basal amount of glucose being released to the liver through gluconeogenesis[2] sets the new steady state value of a diabetic individual to one that is closer to healthy levels. Every glucose peak following a meal would be lower which would drive the body to healthy levels.

Literature study produced two papers that researched and proposed their version of a metformin pharmacokinetic and pharmacodynamics models. Meibohm and Derendorm defined the basic concepts of pharmacokinetics as "describing the drug concentration-time courses in body fluids resulting from the administration of a certain drug dose, and pharmacodynamics as the observed effect resulting from a certain drug concentration [8].

Chae et. al. developed a population PK/PD model of metformin using a signal transduction model. The study took forty-two healthy humans, not afflicted with the diabetes, and gave them a traditional 500 mg tablet of metformin [6]. Researchers found the model to be robust utilizing typical biochemical and bioengineering verification techniques. However, this paper utilized common PK/PD equations and modeling techniques which would require extensive study in the field of PK/PD modeling and conversions to integrate within the Cobelli Model.

Sun et. al. produced the most helpful paper for integrating a mathematical model of metformin into Cobelli. In this paper, ordinary differential equations modeled the flow of metformin from ingestion into various regions of the body as a flow in and flow out situation [7]. Figure 6 below visualizes the model by their compartment state and represents its flow through the body.

[2] Gluconeogenesis - is a metabolic pathway that results in the generation of glucose.

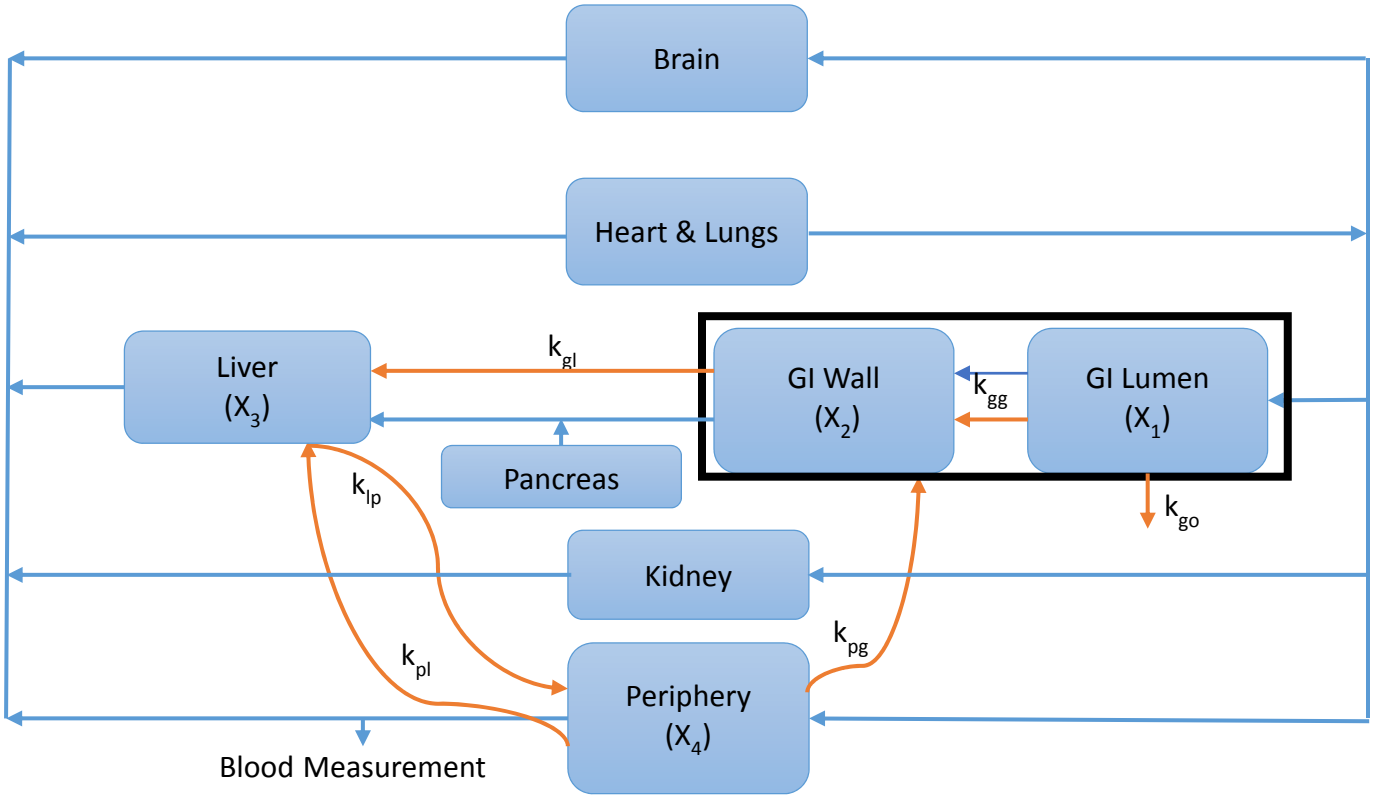

Figure 6: Sun et. al. Metformin PK/PD Model *[7]*

The mathematical model proposed by Sun et. al. represents a physiological simplification of the ingestion of metformin to its effect on the body and its glucose lowering effect. This model is then able to be incorporated as a Simulink Matlab model, which reinforces its feasibility to be integrated within the Cobelli Model. Sun et. al. utilized the Vahidi simplified mathematical model of glucose-insulin interactions to validate their research [7]. The Vahidi model only has three states of glucose, insulin, and glucagon [9]. The Cobelli Model would provide a better representation of how metformin affects human patients once the ordinary differential equations from Sun et. al. is incorporated within the revised Cobelli Model. All the more reason to validate the reason of selecting the Cobelli Model due to its FDA approval as being the most physiologically accurate.

Incorporating Metformin

I. Background Information

Previous research at USNA only considered the modeling of fast-acting and slow-acting insulin, and secretagogues. The modeling of the fourth medication, sensitizing agents, was not considered. To further improve the physiological accuracy of the Cobelli Model, the modeling of metformin was investigated and demonstrated.

Figure 7, represent the overall Cobelli Model and the areas where metformin will affect the human system when comparing the Cobelli paper against Sun's. There are two papers that illustrate the two derived metformin target areas, the endogenous glucose production pathway and the glucose-dependent utilization pathway [6,7]. The glucose utilization on insulin dependence pathway lowers the overall glucose by forcing the body to be more sensitive to insulin and thus opening the cells to uptake more glucose [3,6,7]. Metformin lowers glucose levels through the endogenous glucose production pathway by creating a new glucose minimum for the body to obtain and thus would release less glucose from energy reserves in the body in order to reach the new steady-state value [3,6,7]. The medication either lowers glucose by increasing the body's sensitivity to insulin or by reducing the amount of glucose stores released from the body.

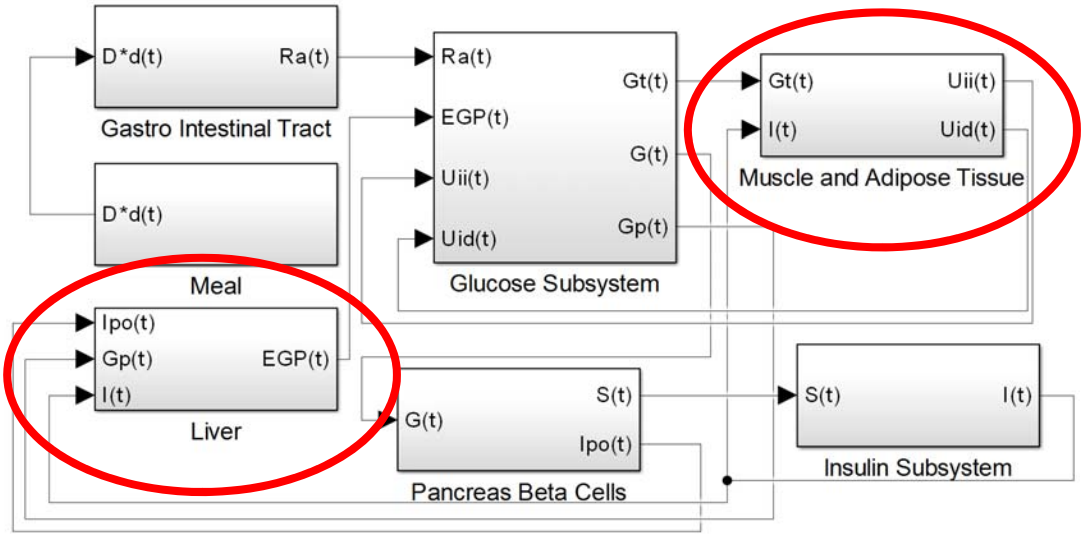

Figure 7: Cobelli Model and circled affected areas

Figure 8 is a schematic of the flow of metformin from oral ingestion to periphery delivery. Upon being ingested into the stomach as an oral mass, it is then absorbed into the GI system, then the liver, ending at the periphery. The medication travels from the outermost layer of the body to the center and then back out [6,7]. The medication will either limit the natural amount of glucose being produced in the body to maintain fasting levels of glucose or increase the amount of glucose utilized to lower the peaks of glucose post-meal [6,7]. To ease the implementation of metformin within the revised Cobelli Model, it was determined that it was impossible to validate

which pathway was the most physiologically accurate without empirical patient data. The glucose utilization insulin-dependent pathway was selected since there was corroboration among two papers regarding the pathway [6,7]. The differential equations determined and presented by Sun et. al. will allow for easier integration and implementation in the Cobelli Model.

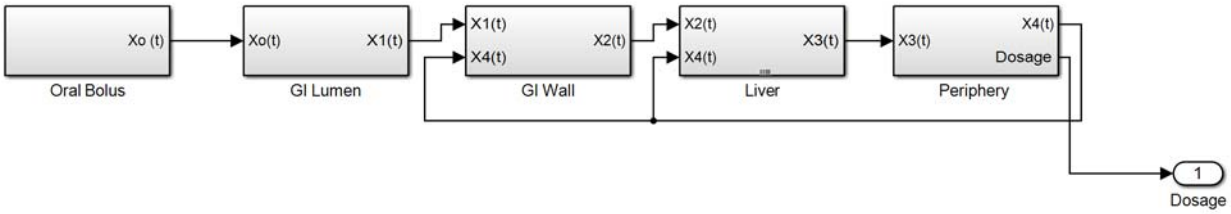

Figure 8: Metformin flow chart from ingestion to absorption, *[7]*.

II. Differential Equation Integration

To integrate the metformin model form Sun et. al., a generic step function was used to simulate metformin's rise and decay which followed traditional first order systems[3]. Utilizing a generic step function allowed for more streamlined parameter testing to determine if they medication pathway stated in L. Sun's paper worked in conjunction with the Cobelli model. Absorption of metformin in the body happens rapidly and has a lower time constant than its excretion [6]. To test the identified metformin effect the ingestion of medication had a time constant that was a sixth smaller, therefore faster, than the excretion time constant. This feature is important for medication, since the patient would want a fast and sustained response. Figure 9 represents that the metformin underwent expected results when testing its dynamics and kinetics within the Cobelli Model. This relates the accuracy of the integration of the differential equations as a Simulink model in comparison to the clinical trials and data [7].

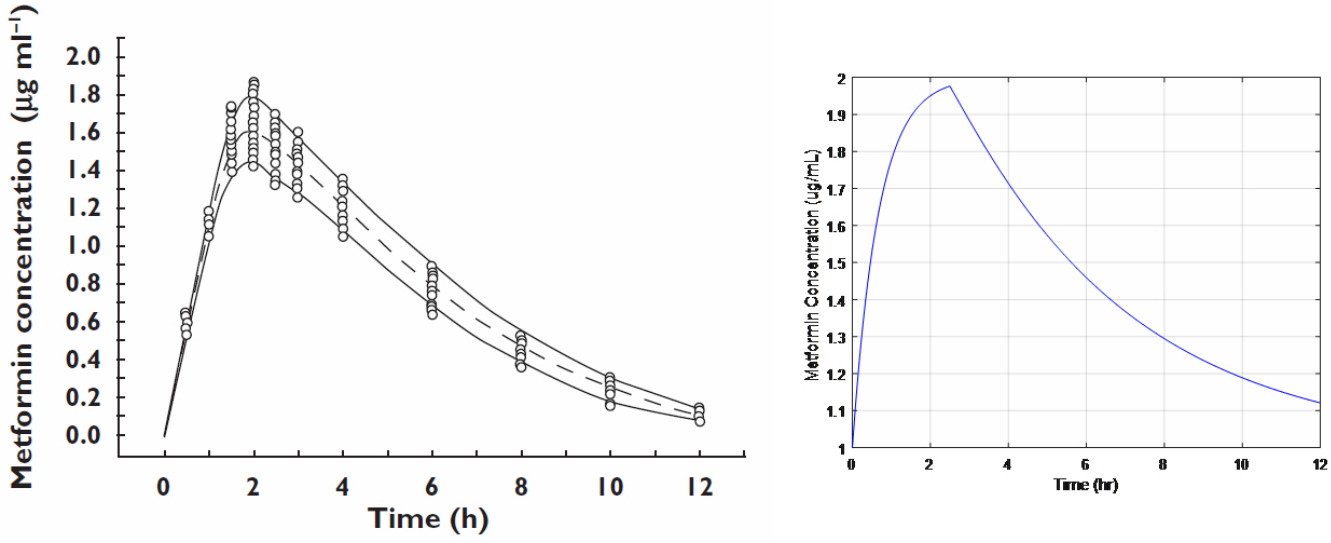

Figure 9: metformin generic absorption test within the Cobelli Model

[3] First order system – a system whose input and output is dependent on a first order differential equation

The glucose lowering effect was also compared to the results presented in Sun et. al. Figure 10 below represent the effects of metformin as presented in literature and contrasted against the investigation from integration within the Cobelli Model. As evident from the comparison of both plots, the results from the integration of metformin within the Cobelli Model which matches well with Sun's results with similar shape and peaks to emulate physiological accuracy.

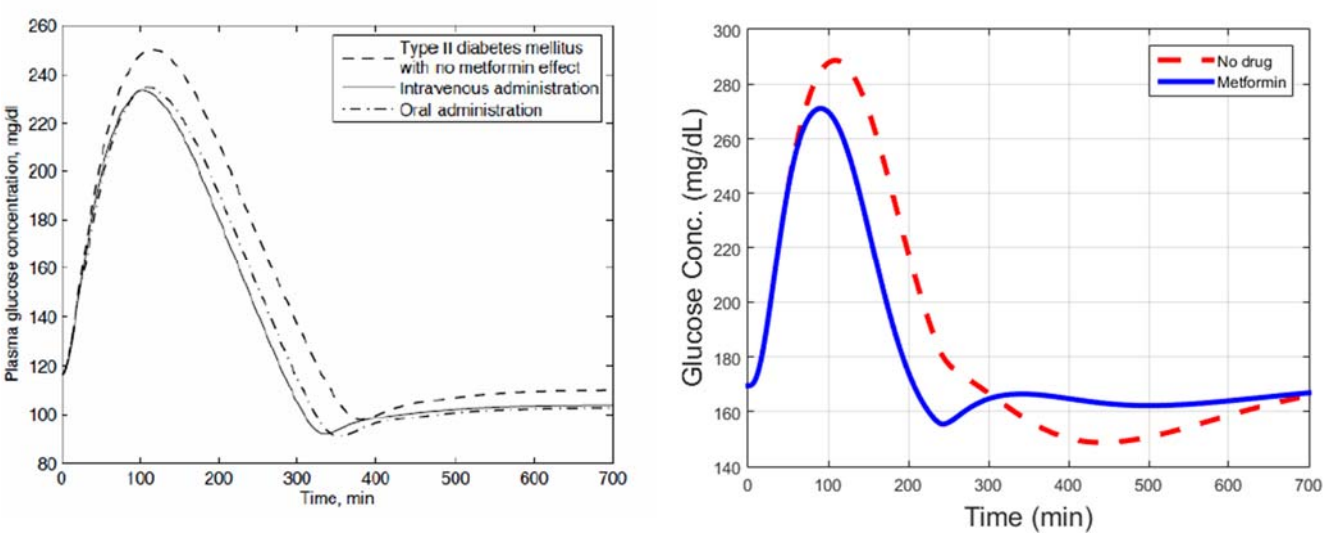

Figure 10: Sun et. al. glucose lowering effect over the course of one meal compared to the incorporated lowering effect within the Cobelli Model *[7]*

III. Drug Dosage Tests

After integrating the metformin differential equations and determining a cost function that would force and limit the dosage of the medication between 500mg to 2000mg and only once a day, the Model Predictive Controller was run to obtain experimental data. Enclosure (5) represents the Model Predictive Controller being run at 2000mg. A single stem on the second plot proves that a cost function could be created that limits the amount of insulin given to once a day. Results from the Model Predictive Controller run with just one medication, represents that the algorithm can be made to administer the dosage once a day. The once a day administration was used for these trials to demonstrate that the controller could emulate the standard method of prescription, before it began to optimize dosage time and sizes.

Utilizing the fact that the incorporated metformin model works within the Model Predictive Controller; further dosage sensitivity tests were performed. Figure 11, below, represents the dosage of metformin being given to the patient as the controller and model performs their iterations. This provides further evidence that glucose utilization insulin-dependent pathway works in lowering diabetic glucose levels with a linear scalability related to drug dosage. The linear scalability of increasing drug dosage makes sense physiologically. If a patient needed to reduce the effects of diabetes, their physician would prescribe a larger prescription.

There was an anomaly after the second or third meal, depending on the dosage, there is an overcorrection of the body to return to a higher glucose level after the medication wears off. The overcorrection is not severe since 10-30 mg/dL over the non-medicated amount cannot be felt by

a diabetic who usually operates at higher glucose levels. Medications are usually accompanied with side-effects, and this may be a side-effect of the drug. It could also be due to residual entries within the state when the differential equations are solved explicitly. However it was theorized that the over-correction was due to the medication delaying insulin production. Thus the patient would not be prepared for the next meal, and once metformin wore off, increased glucose values would occur.

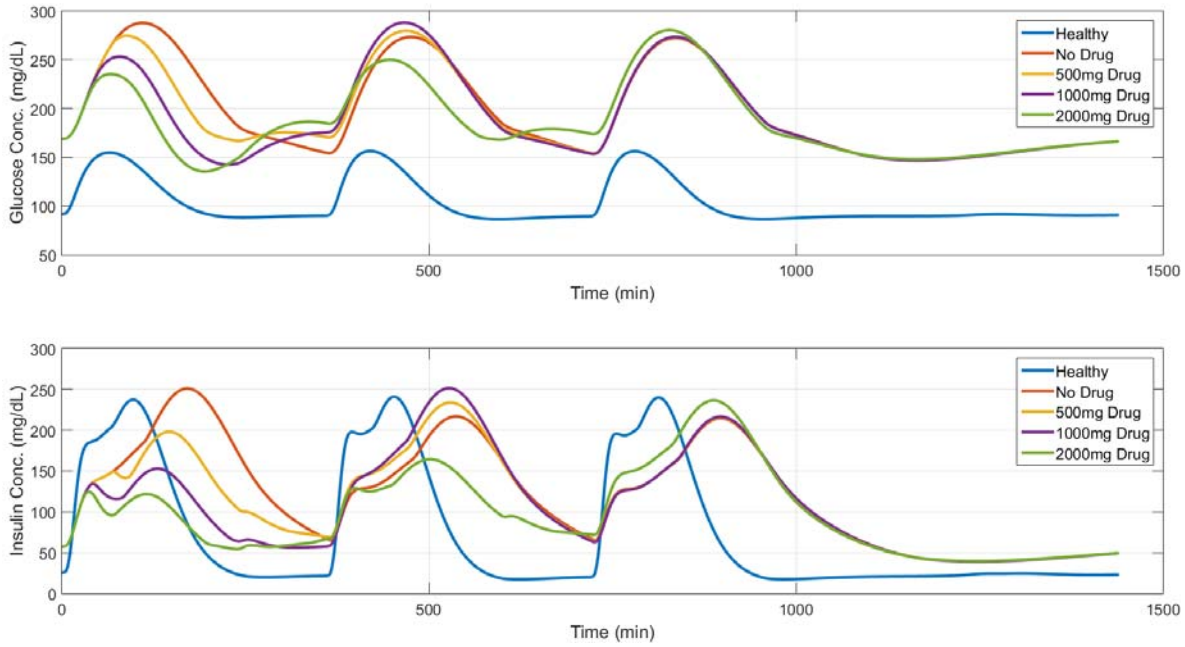

Figure 11: Glucose and insulin data from the Cobelli Model at 500mg, 1000mg, and 2000mg against healthy levels through the glucose utilization insulin dependent pathway

Metformin has been shown to be expanded from its previous validation in Sun et. al.'s research. Cobelli Model results matched the same glucose-lowering effects found in literature [8]. An additional medication to the Cobelli Model further augments its physiological accuracy. Sun et. al. demonstrated that their model was validated clinically through patient data [8]. Thus, the repeating of similar results when incorporated within the Cobelli Model demonstrates that the model has increased its own physiological accuracy. The model now consist of slow-acting, and fast-acting insulin models, a derived secretagogue model, and an expanded metformin model.

Model Predictive Control Development

I. Cost Function Background

The main goal of the research was in regard to the Model Predictive Controller was in the creation of the cost function algorithm, a generic one shown in Equation 1.

$$J = \sum_{n=i}^{k} [q(r_i - y_i)^2 + {u_i}^2]$$

Equation 1: Generic cost function

The engineer adjusts the performance of the AMPC algorithm through a cost function. There are separate cost functions for the parameter adaptation and medication prescription process. The cost function computes a single (scalar) number from the relevant inputs and outputs to the model. In AMPC, an optimization routine chooses the best set of parameters or prescription of medication by minimizing the scalar cost.

A generic control cost function is shown in Equation 1 where r_i is the i^{th} sample (discrete value) of the desired output (healthy blood glucose concentration in this project), y_i is the i^{th} sample of the measured output, u_i is the i^{th} sample of the applied input (medication prescription in this project), and q is the constant weight or penalty factor to be chosen by the engineer. In most engineering problems, a trade-off exists between error, r_i-y_i, and input usage, u_i. To achieve smaller error, more input must be used. The weight, q, allows the engineer to balance these conflicting requirements. If q is chosen to be greater than one, the error is artificially exaggerated. As a result, the generated input will be greater and the error will be smaller than if. Conversely, if q is chosen to be less than one, the generated input will be less than and the error will be greater than if q equals one.

The cost function, with regard to metformin, forced the controller to only give one dose of metformin per day. Also, metformin had to be controlled between the dosages of 500mg and 2000mg since literature and physicians state those are the ranges of metformin medications [3,7,8]. To solve the problem of multiple doses in a day, the weight or q value was greatly increased after the first dose. The range of dosages constraint was enforced in the MPC formalization in the lower bounds and upper bounds of the possible medication dosages.

II. Random Patient Simulation Experiments

Before aggregating all four medications into the Cobelli Model as ordinary differential equations, validation checks were performed using their Simulink block diagram analog. The use of a randomly generated 50 patient batch would test the fidelity of the four medication models among a wide stretch of patient parameters. Enclosure (6) represents a small sample of the four medication tests from mild to severe diabetic Cobelli parameters.

Patients were separated and labeled as mild, medium, or severe diabetic through quantitative and qualitative checks of the plots in Enclosure (6). Mild diabetics have a basal glucose value between 90-120 mg/dL, medium diabetics would have a basal glucose between 120-150 mg/dL, and severe diabetics would have a basal glucose between 150-180 mg/dL. The insulin plots were also included to demonstrate the inverse relationship of glucose and insulin levels.

Visual inspection of the plots in Enclosure (6) corroborates the physiological accuracy of the four medications. By physiological accuracy, in this case it is defined as keeping the patient

within normal ranges of blood glucose while following the pharmacokinetics and pharmacodynamics of the medications from literature.

III. Total Nonlinear Model Predictive Control Algorithm

First, the timing of when to give the long-acting medications, slow-acting insulin and metformin, had to be determined. The injection timing for these two medications would configure the Cobelli Model to give the patient these medications at the best time for an average diabetic patient. Since the Cobelli Model operated on a set of average parameters, both healthy and diabetic patient parameters were the mean of both cases from the Cobelli et. al. paper, [3]. Identifying the best time for injection given average parameters would provide similar results in random patients, assuming the parameters in the Cobelli Model followed a normal Gaussian distribution. Enclosure (7) represents the results from the experiment that took an average diabetic patient and gave one medication at the beginning of the day and moved the ingestion by three hours from 0-18 hours. The medication was moved three hours for each trial since medications take a while to effect the body. A three hour time window would provide enough time for the medications to enter the body and begin to lower blood glucose.

The data from Enclosure (7) was then visual inspected by averaging the local maxima and minima and nothing any significant glucose changes. The best time to administer both medications was metformin at the beginning of the day and slow-acting insulin three hours later. There were other trials that had lower blood glucose values than the selected choice. However, the lower glucose values came with a cost. The cost was the significant drop in glucose after a meal. That significant drop could be disastrous if an individual were to perform strenuous activity since they were approaching healthy range, but their body had yet to stabilize their glucose values before their next meal. Strenuous activity could then shock the body and have the blood glucose drop lower than healthy range leading to hypoglycemia. The robustness of these times was tested in the model fidelity experiments.

Second, the cost associated with “reasonable” fast-acting insulin was performed on a MPC that only had fast-acting insulin as an input. The controller went through a variety of upper-bound dosages and weight combinations until a duo was discovered that did not saturate the inputs. That means the controller did not try and give a full dose for every iteration, rather it decided that it could give half doses in order to keep the minimum blood glucose above the healthy threshold of 120 mg/dL - 90 mg/dL [3].

It is evident that the secretagogue model is not included with the controlling mechanism. Extensive literature research failed to yield a true mathematical model for secretagogues. So, in order to maintain the high physiological accuracy of the Cobelli Model it was excluded from one of the controlled inputs. Adding the derived model would tarnish the physiological accuracy of the research, since using the Cobelli Model set the foundation for physiological accurate results.

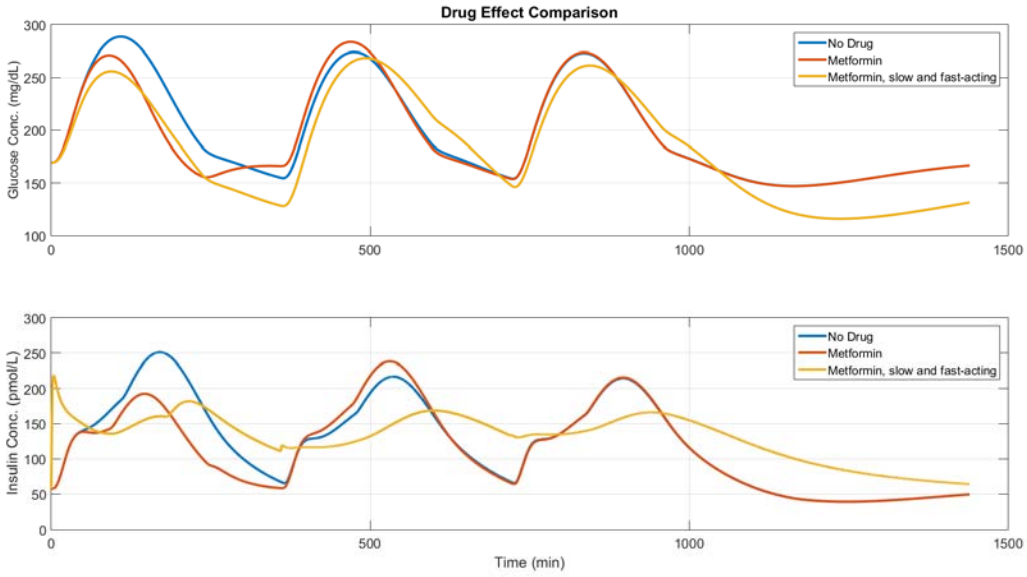

Figure 22: Optimum drug administration using the results from metformin, slow-acting insulin, and fast-acting insulin optimization tests.

The final step was to integrate both the optimum administration times for both metformin and slow-acting insulin with the fast-acting insulin upper-bound and weight combination. Figure 12 represents the data plotted using the optimum timing and upper-bound and weight combination for drug administration utilizing physician prescription methods.

Proof of Concept Experiments

I. Baseline Model Predictive Controller Trials

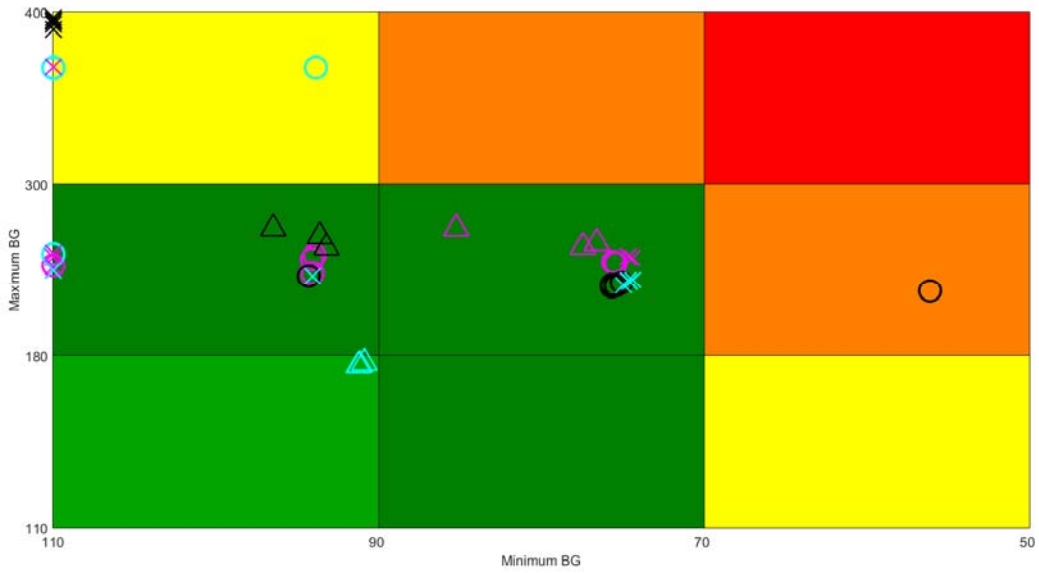

Figure 33: The above figure represents the average set parameters from the Cobelli paper being used and evaluating the effectiveness of the controller against open-loop control and no drug administration, *[5]*. The different colors represent the three different severity types ranging from mild (cyan), medium (magenta), and severe (black). The different markers represent no drug (xs), open-loop control (circles), and closed-loop control (triangles).

Figure 13 visualizes the twenty-one experimental baseline trials among the three methods, no drug, open-loop, and closed-loop to showcase sixty-three experimental data points. There were seven patients tested from each threshold, mild, medium, and severe.

Administering no drugs to any of the randomly generated patients serves as a control to verify drug usage. These results follow common sense in the fact that administering no medication to diabetics would keep their blood glucose levels within unhealthy ranges.

Open-loop control moved the randomly generated patients that fall under mild and medium diabetic categories back into healthier territory, but kept the severe diabetics in unhealthy ranges from differing maximum blood glucose and minimum blood glucose. The open-loop control method represents a traditional prescription for diabetic patients, since it simulates taking medications at the same time every day regardless of meal size and time.

Closed-loop control kept the patients within the healthy ranges for all categories from mild, medium, and severe. The mild patients were in the healthiest range with low maximum blood glucose and higher levels of minimum blood glucose. The severe and medium patients followed suit with the trend of increasing severity leading to increased glucose levels.

The Model Predictive Controller is shown to successfully work with the administering medications and maintain healthy levels when compared to both no drug and open-loop control with all 21 patients within healthy range and only18 of the open-loop control within the same range.

II. Random Patient Meal Times Trials

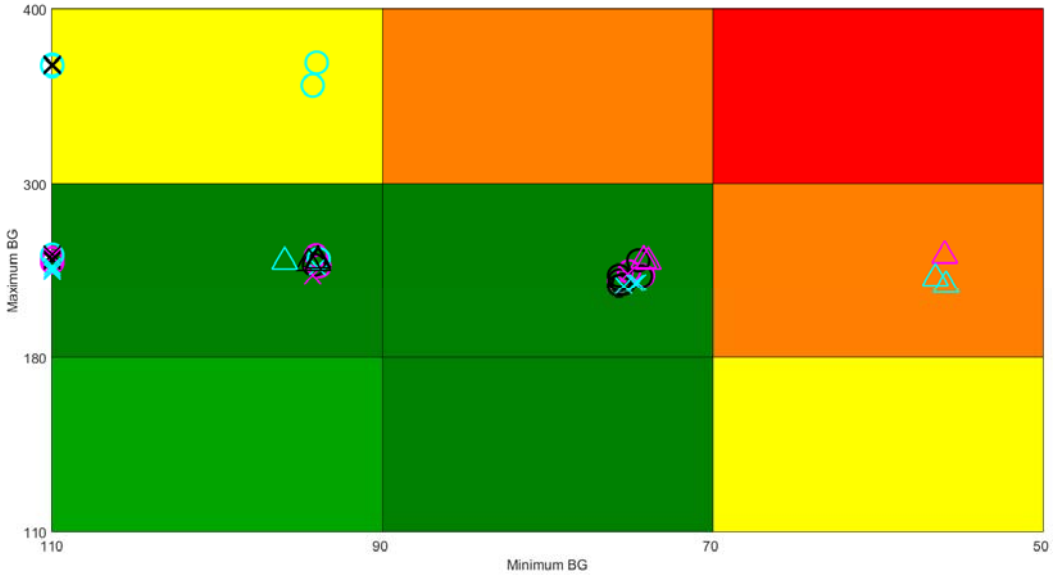

Figure 44: The above figure represents random meal times using random patient parameters to evaluate the effectiveness of the controller against open-loop control and no drug administration, [3]. The different colors represent the three different severity types ranging from mild (cyan), medium (magenta), and severe (black). The different markers represent no drug (xs), open-loop control (circles), and closed-loop control (triangles).

Figure 14 visualizes the twenty-one experimental trials among the three methods, no drug, open-loop, and closed-loop to showcase sixty-three experimental data points. There were seven patients tested from each threshold, mild, medium, and severe.

Administering no drugs to any of the randomly generated patients keeps their minimum blood glucose in a healthy level but their maximum blood glucose in the diabetic region. These results, again, serve as an analog to compare the open-loop control and closed-loop control methods.

The random meal times seemed to serve little effect to the closed-loop control method. This was predicted since the model predictive controller was reacting to the predicted meal times rather than the meal sizes. Another reason could be that the model also identified the same meal times and thus could accurately predict the optimal dosage to give the “virtual” patient. However a key thing to note is that the open-loop control kept all the “virtual” patients within close proximity to one another. Unlike the previous experiment the closed-loop and open-loop control had 18 patients within healthy range, the closed-loop had a decreased performance for these trials. This may be due to the controller only optimizing the fast-acting insulin input and not slow-acting insulin and metformin. There should be an increased performance from the closed-loop controller if all three medications were optimized.

Given the above results, the model predictive controller is shown to be validated when meals were randomly assigned rather than pre-determined times throughout the day. It follows average human behavior since people normally do not plan their meals in advance, unless they are on a strict schedule or diet. This experiment showcases the behavior that is typical of a person throughout a day, assuming they eat roughly the same meal size for all three meals.

III. Random Patient Meal Size Trials

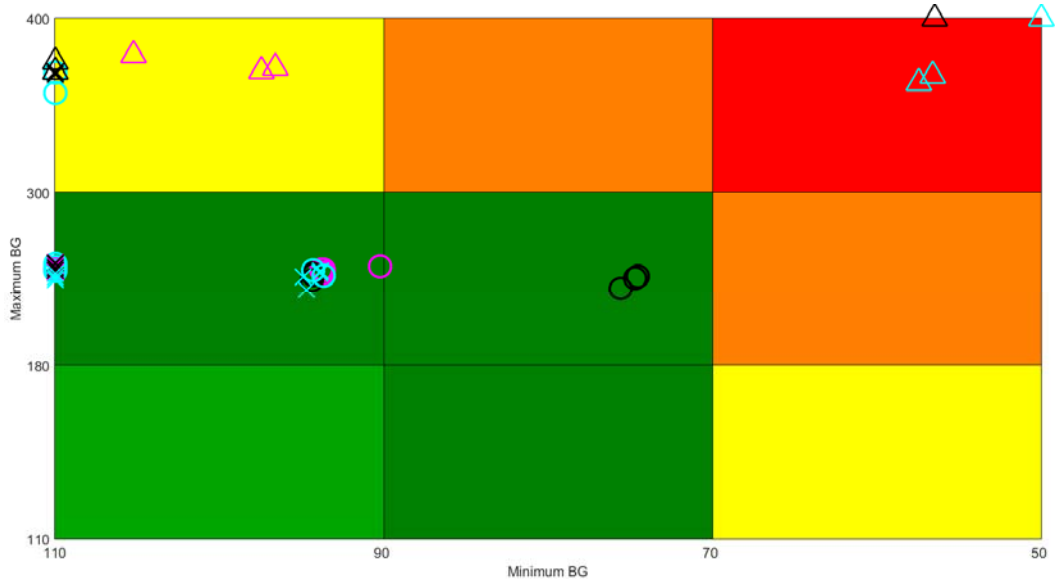

Figure 155: The above figure represents random meal sizes using random patient parameters to evaluate the effectiveness of the controller against open-loop control and no drug administration, [3]. The different colors represent the three different severity types ranging from mild (cyan), medium (magenta), and severe (black). The different markers represent no drug (xs), open-loop control (circles), and closed-loop control (triangles).

Figure 15 visualizes the twenty-one experimental trials among the three methods, no drug, open-loop, and closed-loop to showcase sixty-three experimental data points. There were seven patients tested from each threshold, mild, medium, and severe.

Once again, the no drug group serves as the analog control group for the experiment to determine if closed-loop is better or worse than open-loop.

The random meal sizes proved troublesome for the model predictive controller. However, the problem lies with the experimental procedure rather than the controller itself. In the experiment, a total meal size for the day was determined to be three times the average meal size from the baseline tests. Then the meals throughout the day would be randomly generated and all three meals would equate to the total meal size, therein lies the source of the error. There may be times when people eat large meals every once in a while, but the average person does not skip two meals to eat the equivalent of all three meals in one sitting. It can be argued that diabetic patients are not your average person, but there is a counter-argument stating that the average diabetic patient would not skip two meals to gorge themselves on a single meal.

A follow-on researcher could improve upon this fidelity test to determine the meal sizes that best determine the normal range of a “light” meal and the upper-bound of a “heavy” meal. Once those lower-bounds and upper-bounds are determined, the model predictive controller can be truly tested.

Conclusions and Recommendations for Future Work

The two primary objectives of integrating an additional medication to the Cobelli Model, and developing the controller algorithm were met. Prior to this year, the model already had slow-acting and fasting-acting insulin, and a derived secretagogue model. To further the physiological accuracy of the model, metformin equations were added to augment the model with another medication that physicians typically prescribe for diabetic patients. The controller algorithm was the significant portion of the research this year since it was what made the decisions of the size of medication dosages to apply and when to administer them. The closed-loop control performed better than the open-loop, physician method, with more patients within healthy range; the only exception being the random meal size experiments. By the end of the year, a framework for testing and developing different methods and medication prescriptions was created. Once patient data is able to be accessed, the physiological accuracy of the different medications could be validated across all ranges of applicability. Assuming patient data becomes available, the model predictive controller can be used to augment physician prescriptions.

Diabetes has been a heavily researched medical topic within the Systems Engineering Department. The Cobelli Model has been expanded upon the modeling of slow-acting, and fast-acting insulin, and secretagogues to include metformin and the creation of a optimizing algorithm. A follow-on researcher will be able to take the current state of the model and integrate both the adaptive portion of the controller with the derived algorithm to test the fidelity of the adaptive portion when used in conjunction with the algorithm. Continued research endeavors under the council of Professor O'Brien will further develop the model predictive controller for development towards an artificial pancreas in the future.

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Enclosure (4): Metformin Ordinary Differential Equations

```
function stateReturn = Cobelli_total_equations(t,state, Parameters)

% function stateReturn = Cobelli_metformin_equations(t, state, Parameters)
% Conversion from micro-U/ml to pmol/l
% Use alpha = 1 to compare to results in Li-Kuang paper
%alpha = 1;
conv_ins = 1.44e-7; %1.44e-7*7.5E5;% 0.144 micro-U/ml = 1 pmol/l
% Insulin Normalizing Factor

%Pick off Parameters for use in Cobelli model
%Tstep = 0.01; %how do we tell the model how long to run?
%   Glucose Kinetics
Vg = Parameters(1);
k1 = Parameters(2);
k2 = Parameters(3);
%   Renal Excretion
ke1 = Parameters(4);
ke2 = Parameters(5);
%   Insulin Kinetics
Vi = Parameters(6); %note: Vi in Weisberg
m1 = Parameters(7);
m2 = Parameters(8);
m4 = Parameters(9);
m5 = Parameters(10);
m6 = Parameters(11);
HEb = Parameters(12); % where is this used?
%   Rate of Appearance - Gastro Intestinal Tract
kmax = Parameters(13);
kmin = Parameters(14);
kabs = Parameters(15);
kgri = Parameters(16);
f = Parameters(17);
a = Parameters(18);
b = Parameters(19);
c = Parameters(20);
d = Parameters(21);
%   Endogenous Production - Liver
kp1 = Parameters(22);
kp2 = Parameters(23);
kp3 = Parameters(24);
kp4 = Parameters(25);
ki = Parameters(26);
%   Utilization - muscle and adipose tissue
Fcns = Parameters(27);
Vm0 = Parameters(28);
Vmx = Parameters(29);
Km0 = Parameters(30);
p2u = Parameters(31);
%   Secretion
K = Parameters(32);
alpha = Parameters(33);
```

```
Beta = Parameters(34); %note: different than weisberg
gamma = Parameters(35); %note: different than weisberg
```

```
run Metformin_Parameter_Vector

%Metformin Parameters
A_exp = Parameters_met(1);
B_exp = Parameters_met(2);
C_exp = Parameters_met(3);
A_p_exp = Parameters_met(4);
B_p_exp = Parameters_met(5);
alpha1 = Parameters_met(6);
beta1 = Parameters_met(7);
gamma1 = Parameters_met(8);
alpha_p = Parameters_met(9);
beta_p = Parameters_met(10);
k_go = Parameters_met(11);
k_gg = Parameters_met(12);
k_gl = Parameters_met(13);
k_lp = Parameters_met(14);
k_pl = Parameters_met(15);
k_pg = Parameters_met(16);
k_po = Parameters_met(17);
% Conversion for scale factor
conv_met = 7.2/1421.2;



% Prof O'Brien change 18 Nov
BW = Parameters(36);
D = Parameters(37);
Ib = Parameters(38);
Sb = Parameters(39);
h = Parameters(40);
meal = Parameters(41);
```

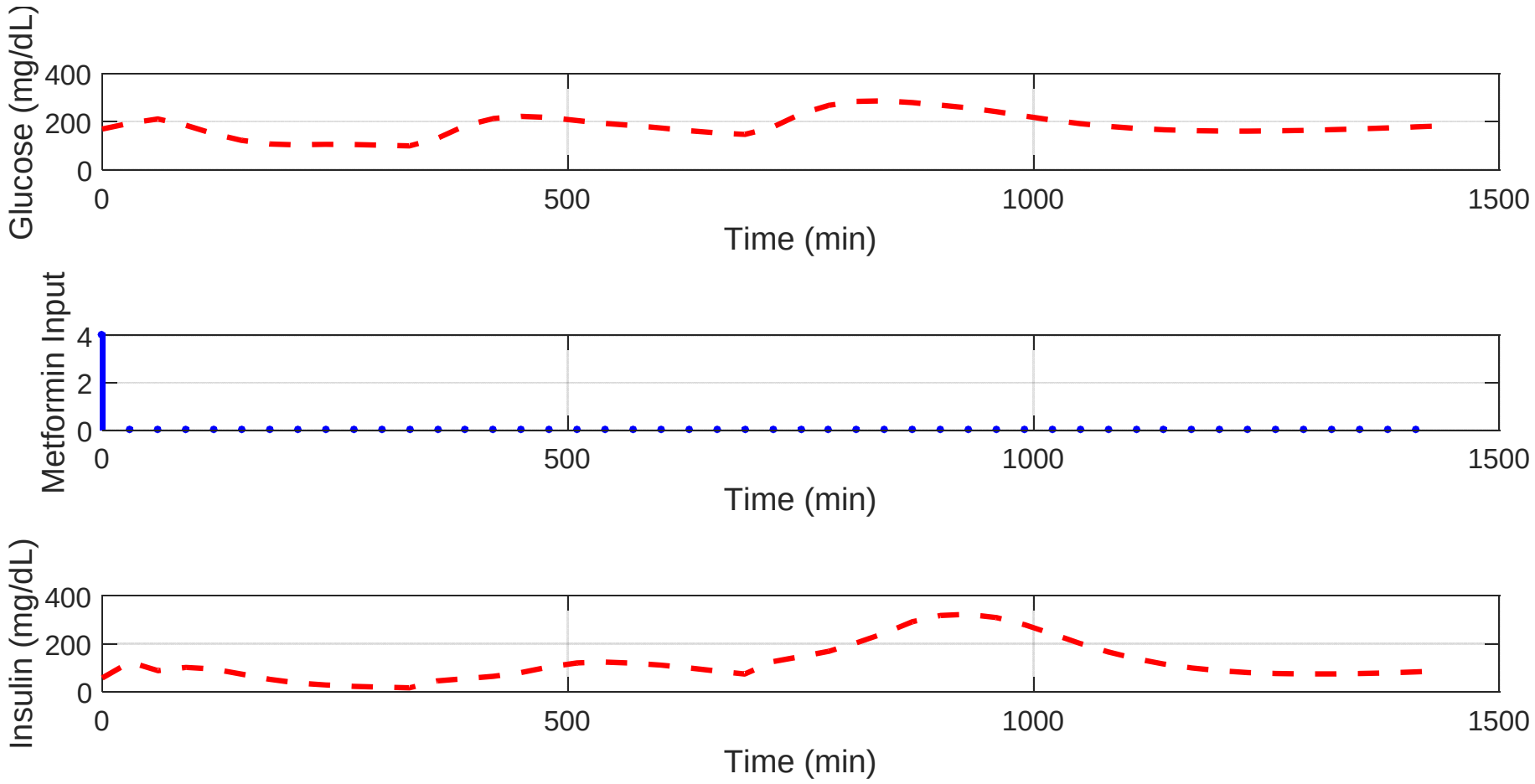
```
%Rate of Appearance
Qsto1 = state(1);
Qsto2 = state(2);
Qgut = state(3);
I1 = state(4);
Id = state(5); %delayed insulin signal
Ip = state(6);%plasma insulin concentration
Ipo = state(7);
X = state(8); %interstitial insulin (muscle and adipose)
Gp = state(9);
Gt = state(10);
Y = state(11);
Il = state(12);
GIl = state(13);
GIw = state(14);
Liv_met = state(15);
Perip_met = state(16);
```

```
Oral_mass1 = state(17);
Oral_mass2 = state(18);
B = state(19);
Hslow = state(20);
Dslow = state(21);
Islow = state(22);
Hfast = state(23); %fast acting insulin
Dfast = state(24);
Ifast = state(25);
```

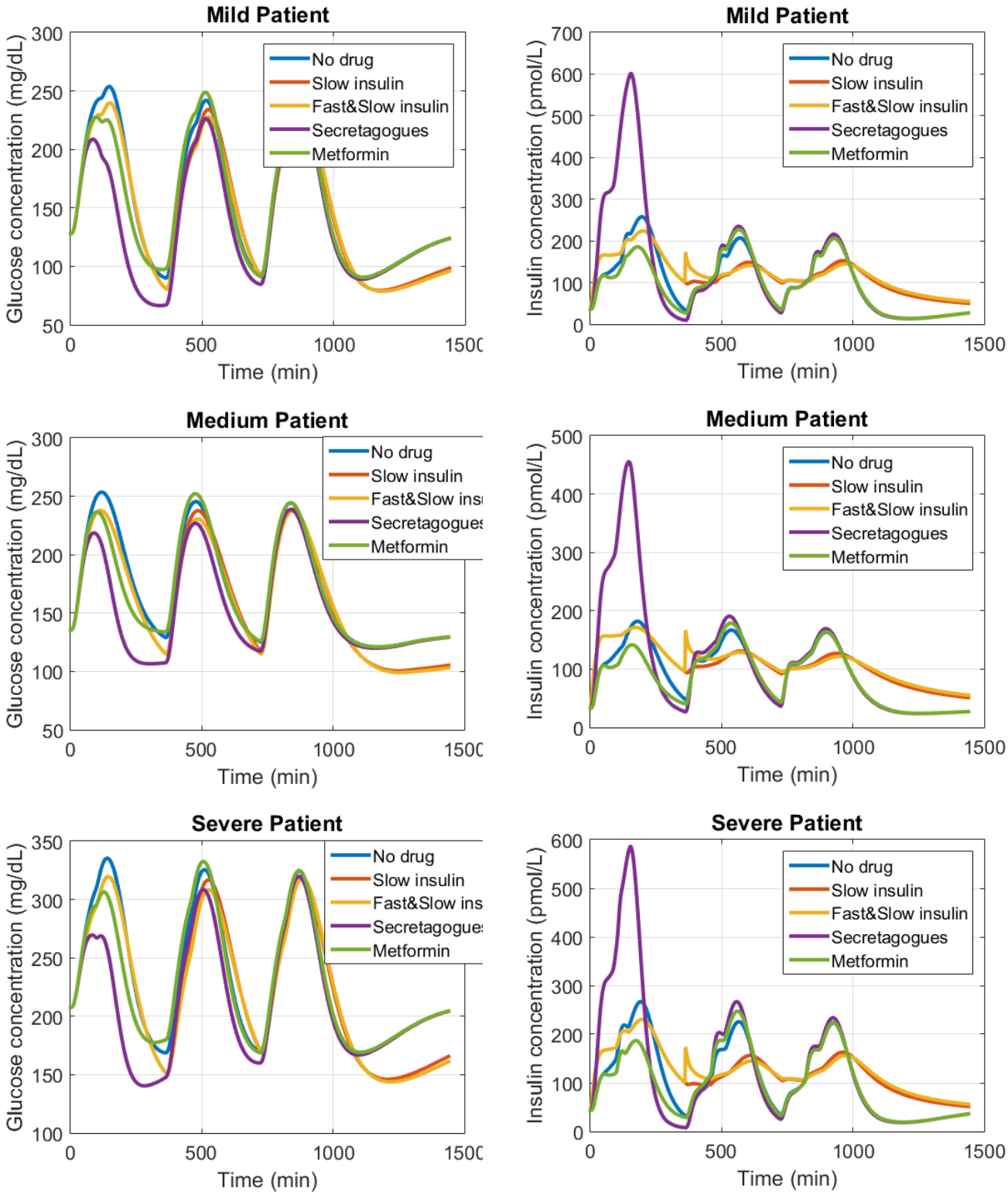
```
%Rate of Appearance
Qsto=Qsto1+Qsto2;
KemptQsto=kmin+(kmax-kmin)/2*(tanh(a*(Qsto-b*D))-tanh(c*(Qsto-d*D))+2);
dQsto1=-kgri*Qsto1;
dQsto2=-KemptQsto*Qsto2+kgri*Qsto1;
dQgut=-kabs*Qgut+KemptQsto*Qsto2;
Ra=(f*kabs*Qgut)/BW;

%Liver
I=Ip/Vi;
dI1=-ki*(I1-I);
dId=-ki*(Id-I1);
EGP=kp1-kp2*Gp-kp3*Id-kp4*Ipo;

%Metformin Dynamics
dOral_mass1 = -alpha_p*Oral_mass1;
dOral_mass2 = -beta_p*Oral_mass2;
dGIl = -GIl*(k_go+k_gg)+ (A_p_exp*Oral_mass1 - B_p_exp*Oral_mass2);
dGIw = GIl*k_gg+Perip_met*k_pg-GIw*k_gl;
dLiv_met = GIw*k_gl+Perip_met*k_pl-Liv_met*k_lp;
dPerip_met = Liv_met*k_lp-Perip_met*(k_pl+k_pg+k_po);


% fast acting insulin parameters
% Converted for use in Cobelli (pmol/l)
p = 0.5;
qf = 0.13*conv_ins^2;
bf = 0.0068;
r = 0.2143;
dif = 0.081;


%Slow acting insulin parameters

k = 2.35E-5;%;0.0000235;
qs = 3.04*conv_ins^2;
bs = 0.02;

dis = 0.0215;
cmax = 15;

%Muscle and Adipose Tissue
dX=-p2u*X+p2u*(I-Ib);
VmX=Vm0+Vmx*X*(max(Perip_met*conv_met,1));
```

```
Uid = VmX*Gt/(Km0+Gt);
dUid = (VmX*Gt)/ (Km0+Gt)^2;
Uii=Fcns;

%Glucose Kinetics
if (Gp>ke2)
    E=ke1*(Gp-ke2);
else
    E=0;
end
dGp=EGP+Ra-Uii-E-k1*Gp+k2*Gt;
dGt=-Uid+k1*Gp-k2*Gt;
G=Gp/Vg;
dG=dGp/Vg;


%Pancreas
    %static secretion
if(Beta*(G-h)>=-Sb)
    dY=-alpha*(Y-Beta*(G-h));
elseif (Beta*(G-h) < -Sb)
    dY=-alpha*Y-alpha*Sb;
end

    %dynamic secretion
if(dG>0)
    Spo=Y+K*dG+Sb;
else
    Spo=Y+Sb;
end

% Normal secretion
dIpo=-gamma*Ipo+Spo;
S=gamma*Ipo;

%Insulin Dynamics
HE=-m5*S+m6;
m3=HE*m1/(1-HE);
dIl=-(m1+m3)*Il+m2*Ip+S;
dIp=-(m2+m4)*Ip+m1*Il+Vi*dIslow+Vi*dIfast; %add fast and slow insulin injections

stateReturn=[dQsto1;dQsto2;dQgut;dI1;dId;dIp;dIpo;dX;dGp;dGt;dY;dIl;dGIl;dGIw;dLiv_met;dPerip_met
;dOral_mass1; dOral_mass2;dB;dHslow;dDslow;dIslow;dHfast;dDfast;dIfast];

end
```

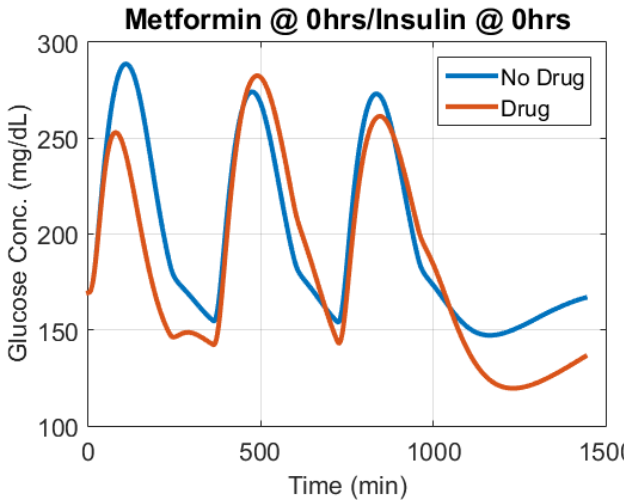
Enclosure (5): Model Predictive Control Metformin Trial

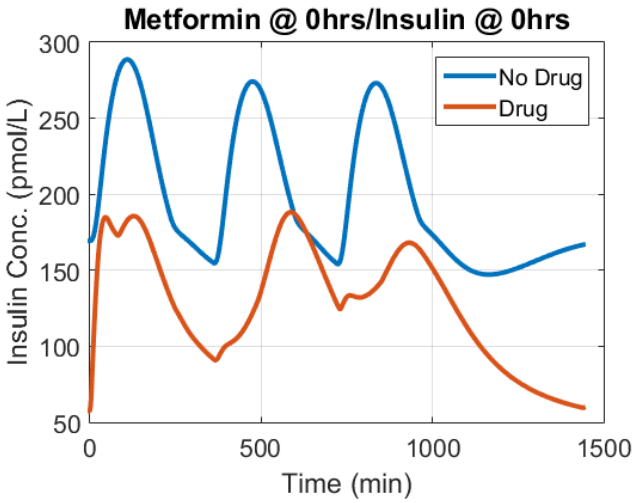


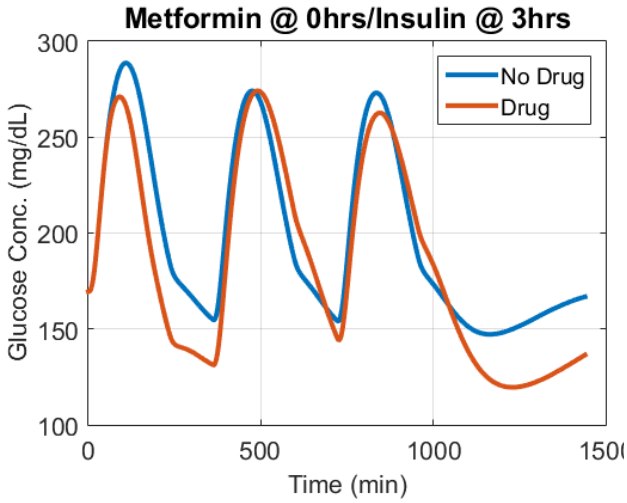
Enclosure (6): Random Patient Parameter Simulation Verification Test

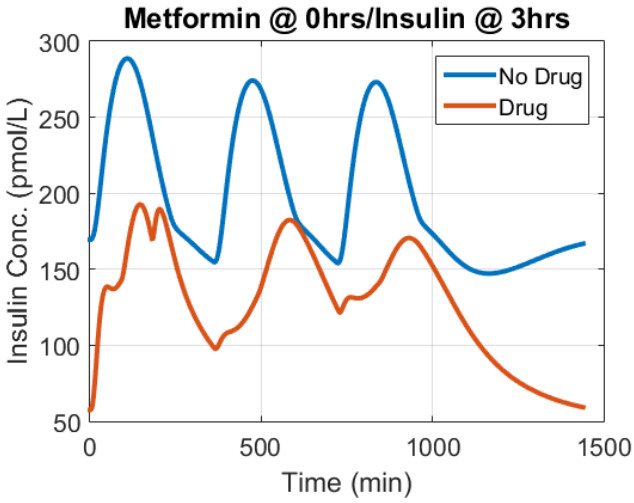


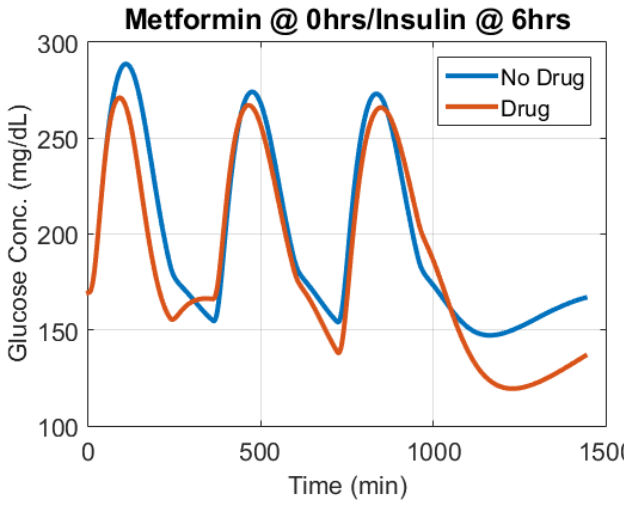
Enclosure (7): Metformin and Slow-acting Insulin Timing Tests

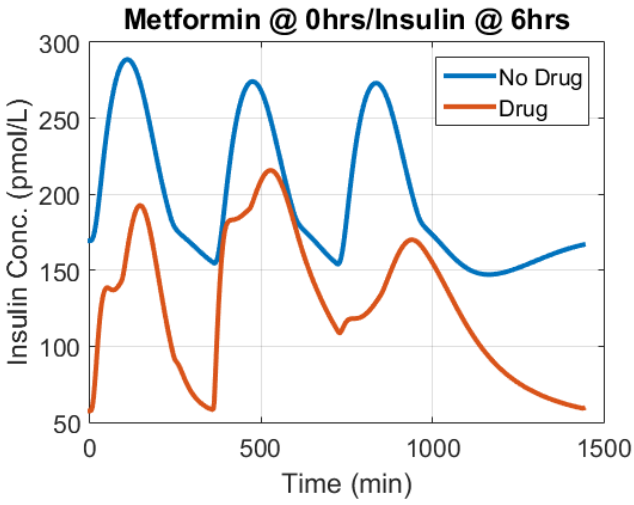


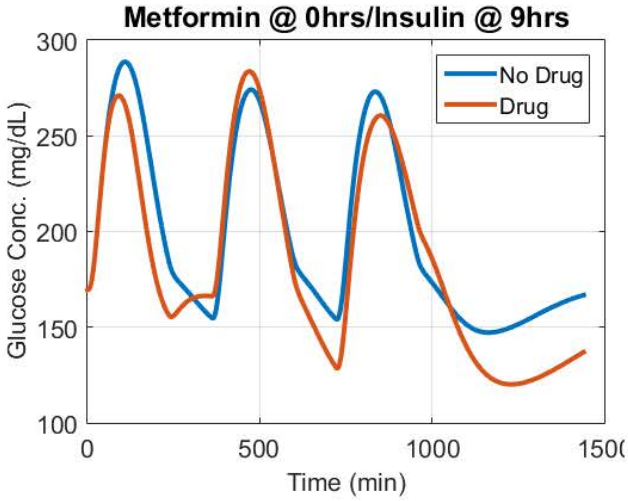


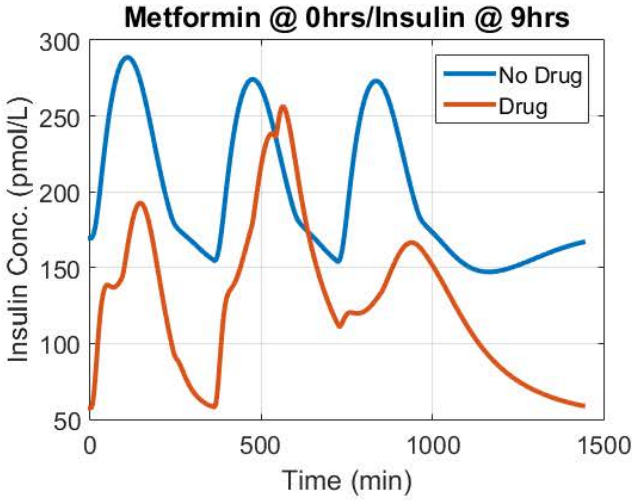


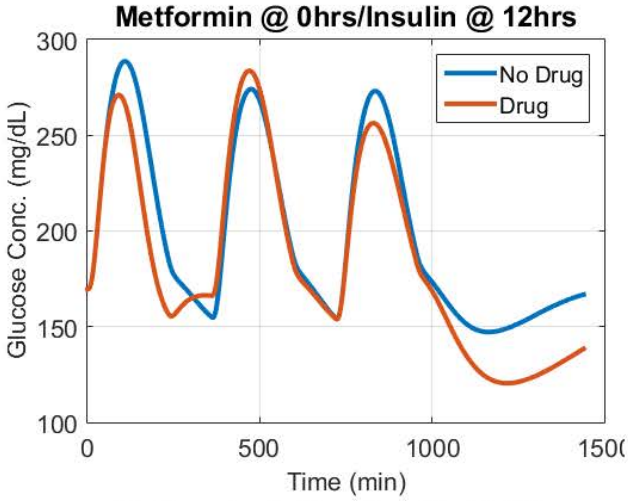


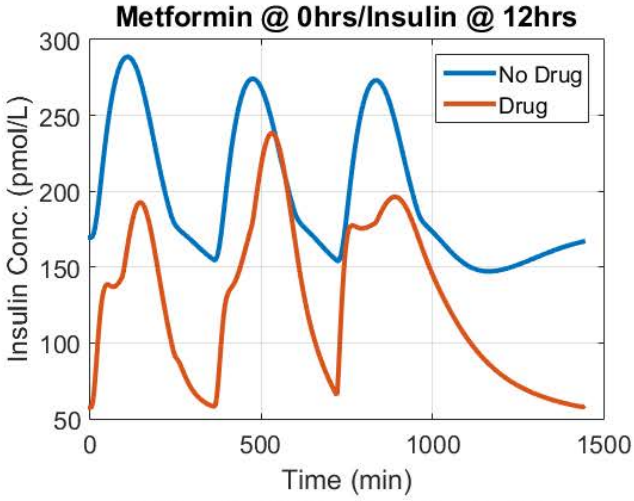


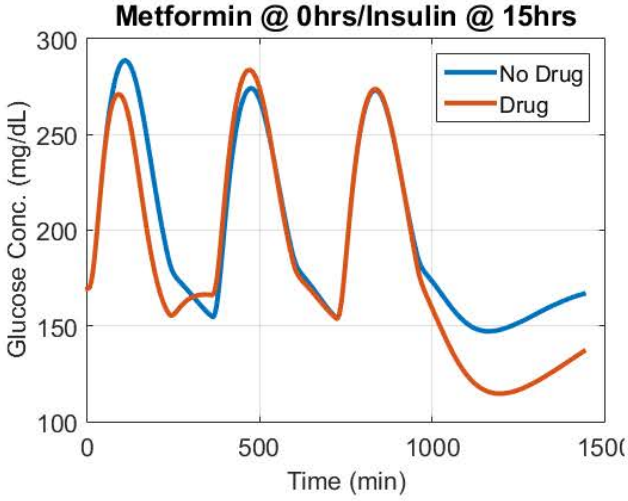


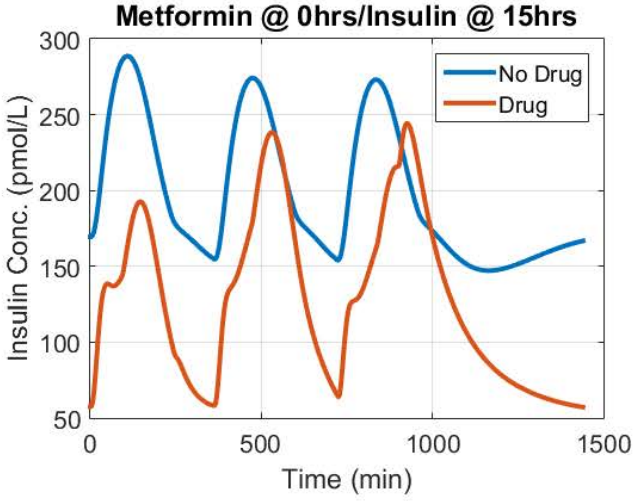

Metformin @ 0hrs/Insulin @ 9hrs
Glucose Conc. (mg/dL)
Time (min)
No Drug
Drug

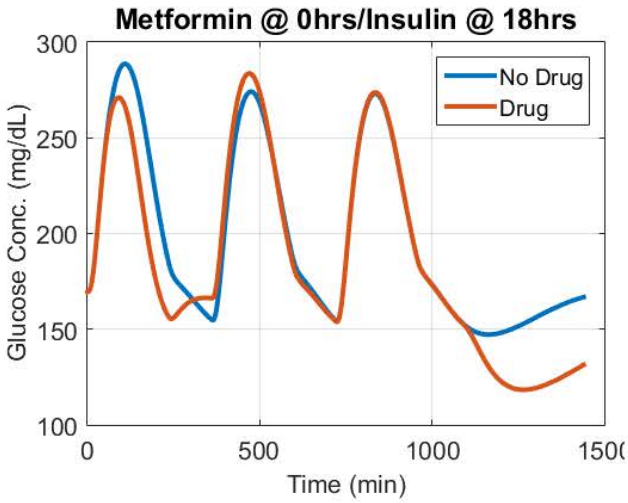

Metformin @ 0hrs/Insulin @ 9hrs
Insulin Conc. (pmol/L)
Time (min)
No Drug
Drug

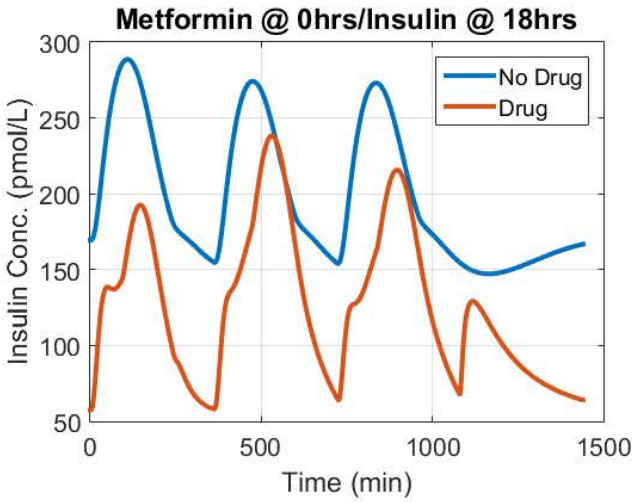

Metformin @ 0hrs/Insulin @ 12hrs
Glucose Conc. (mg/dL)
Time (min)
No Drug
Drug

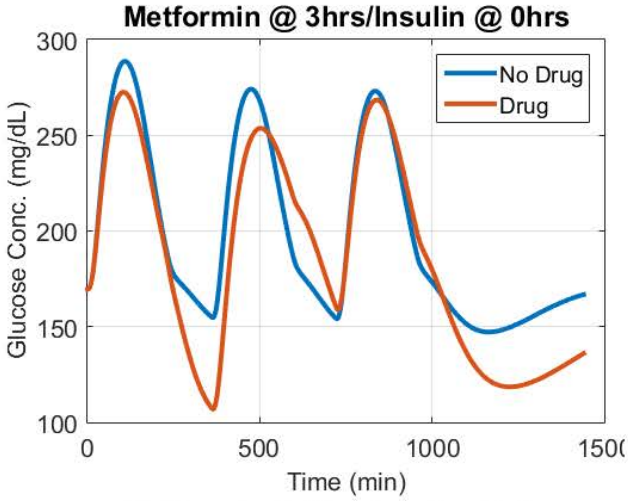

Metformin @ 0hrs/Insulin @ 12hrs
Insulin Conc. (pmol/L)
Time (min)
No Drug
Drug

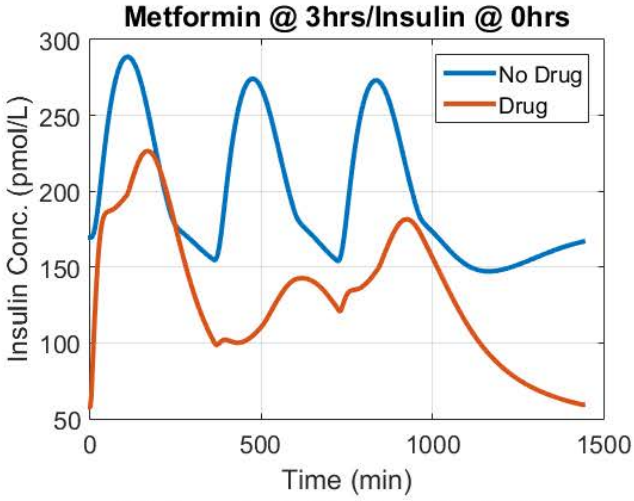

Metformin @ 0hrs/Insulin @ 15hrs
Glucose Conc. (mg/dL)
Time (min)
No Drug
Drug

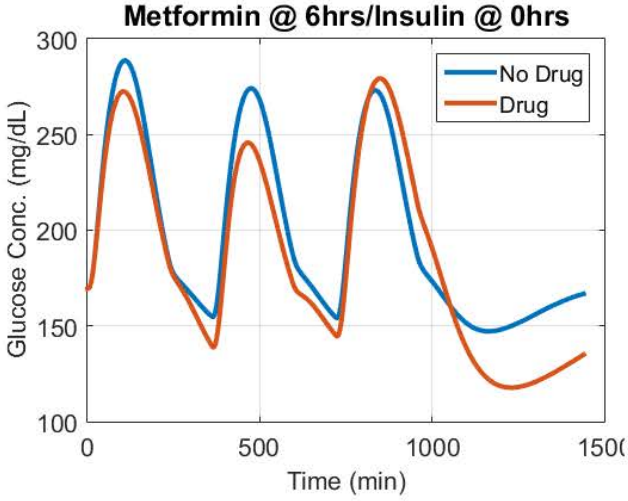

Metformin @ 0hrs/Insulin @ 15hrs
Insulin Conc. (pmol/L)
Time (min)
No Drug
Drug

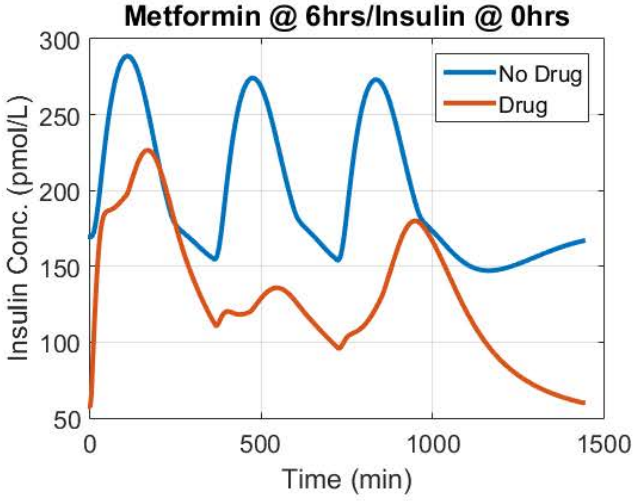

Metformin @ 0hrs/Insulin @ 18hrs
Glucose Conc. (mg/dL)
Time (min)
No Drug
Drug

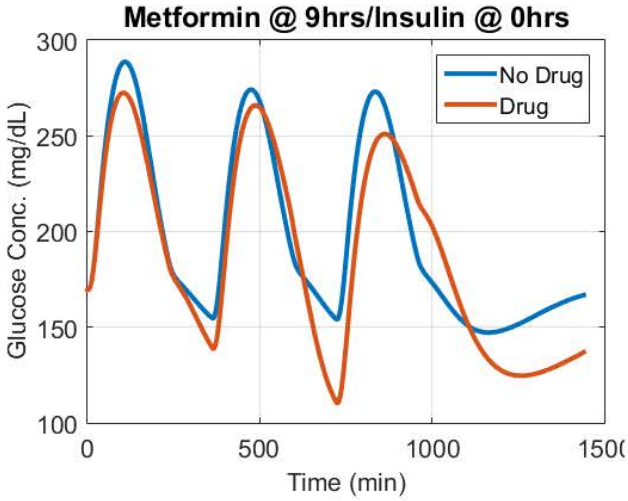

Metformin @ 0hrs/Insulin @ 18hrs
Insulin Conc. (pmol/L)
Time (min)
No Drug
Drug

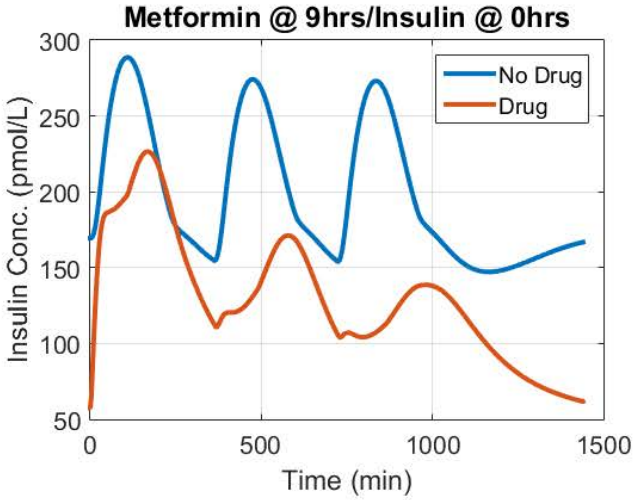

Metformin @ 3hrs/Insulin @ 0hrs
Glucose Conc. (mg/dL)
Time (min)
No Drug
Drug

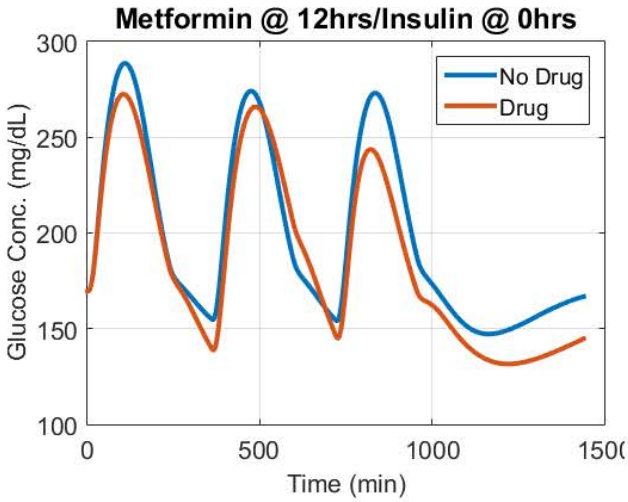

Metformin @ 3hrs/Insulin @ 0hrs
Insulin Conc. (pmol/L)
Time (min)
No Drug
Drug

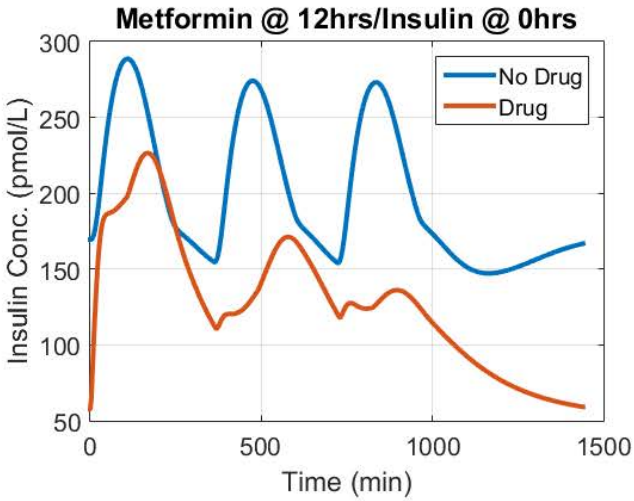

Metformin @ 6hrs/Insulin @ 0hrs
Glucose Conc. (mg/dL)
Time (min)
No Drug
Drug

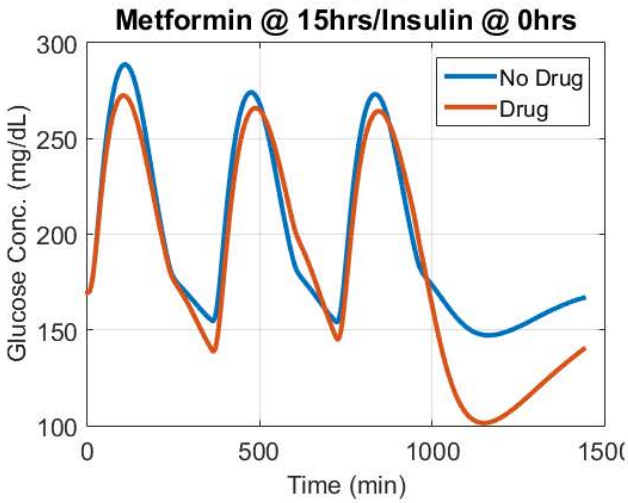

Metformin @ 6hrs/Insulin @ 0hrs
Insulin Conc. (pmol/L)
Time (min)
No Drug
Drug

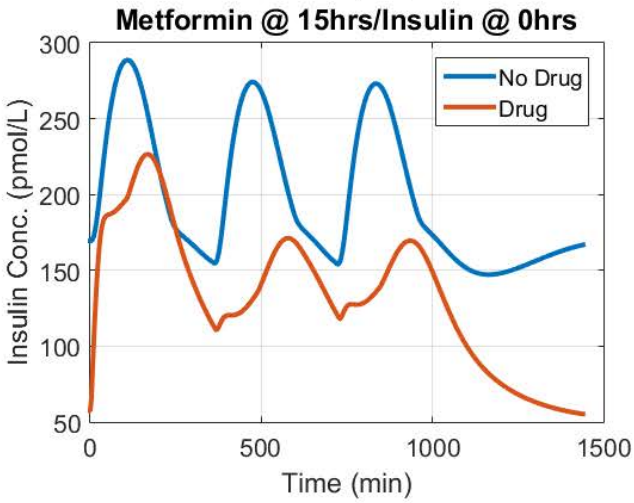

Metformin @ 9hrs/Insulin @ 0hrs
No Drug
Drug
Glucose Conc. (mg/dL)
Time (min)
300
250
200
150
100
0
500
1000
1500

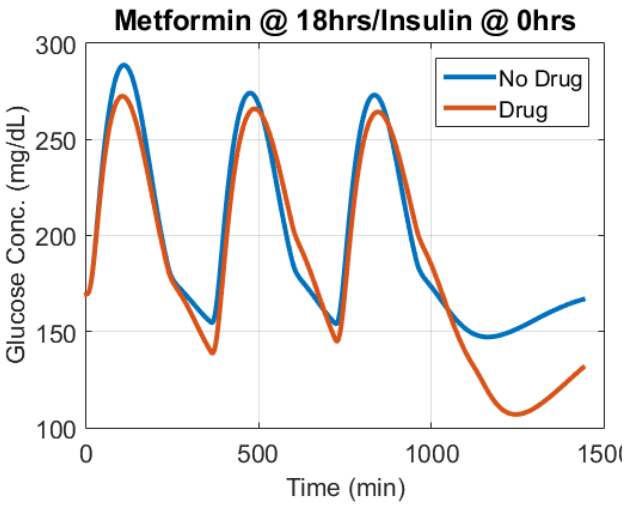

Metformin @ 9hrs/Insulin @ 0hrs
No Drug
Drug
Insulin Conc. (pmol/L)
Time (min)
300
250
200
150
100
50
0
500
1000
1500

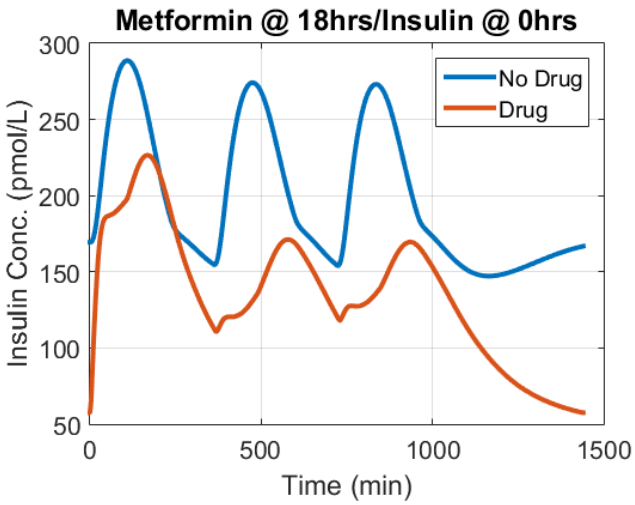

Metformin @ 12hrs/Insulin @ 0hrs
No Drug
Drug
Glucose Conc. (mg/dL)
Time (min)
300
250
200
150
100
0
500
1000
1500


Metformin @ 12hrs/Insulin @ 0hrs
No Drug
Drug
Insulin Conc. (pmol/L)
Time (min)
300
250
200
150
100
50
0
500
1000
1500


Metformin @ 15hrs/Insulin @ 0hrs
No Drug
Drug
Glucose Conc. (mg/dL)
Time (min)
300
250
200
150
100
0
500
1000
1500


Metformin @ 15hrs/Insulin @ 0hrs
No Drug
Drug
Insulin Conc. (pmol/L)
Time (min)
300
250
200
150
100
50
0
500
1000
1500


Metformin @ 18hrs/Insulin @ 0hrs
Glucose Conc. (mg/dL)
Time (min)
No Drug
Drug
300
250
200
150
100
0
500
1000
150(


Metformin @ 18hrs/Insulin @ 0hrs
Insulin Conc. (pmol/L)
Time (min)
No Drug
Drug
300
250
200
150
100
50
0
500
1000
1500